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ORIGINAL CONTRIBUTION

Longitudinal outcomes of children with pediatric autoimmune neuropsychiatric disorder associated with streptococcal infections (PANDAS)

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Abstract Little is known about the natural history of children with pediatric autoimmune neuropsychiatric disorder associated with streptococcal infections (PANDAS). This study prospectively followed 33 children with PANDAS for up to 4.8 years (mean 3.3 ± 0.7 years) after enrollment in a 24-week randomized, double-blind, placebo-controlled trial of intravenous immunoglobulin (IVIG) ($N = 35$). Fourteen of eighteen children randomized to placebo received open label IVIG 6 weeks after the blinded infusion, so follow-up results reported below largely reflect outcomes in a population of children who received at least one dose of IVIG. Telephone interviews with the parents of participants found that at the time of phone follow-up, 29 (88%) were not experiencing clinically significant obsessive–compulsive symptoms. During the interim period (6–57 months after entering the clinical trial), 24 (72%) had experienced at least one exacerbation of PANDAS symptoms, with a median of one exacerbation per child (range 1–12; interquartile range 0–3). A variety of treatment modalities, including antibiotics, IVIG, psychiatric medications, cognitive behavioral therapy, and others, were used to treat these exacerbations, and were often used in combination. The outcomes of this cohort are better than those previously reported for childhood-onset OCD, which may support conceptualization of PANDAS as a subacute illness similar to Sydenham chorea. However, some children developed a chronic course of illness, highlighting the need for research that identifies specific symptoms or biomarkers that can be used to predict the longitudinal course of symptoms in PANDAS.

Keywords PANDAS · Pediatric OCD · Parent interview · Longitudinal study

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Introduction

First described in 1998, pediatric autoimmune neuropsychiatric disorder associated with streptococcal infections (PANDAS) is characterized by (1) the presence of obsessive–compulsive disorder (OCD) and/or a tic disorder, (2) pre-pubertal onset, (3) acute onset and relapsing–remitting symptom course, (4) temporal association with Group A beta-hemolytic streptococcal (GAS) infections, and (5) association with neurological abnormalities [1, 2]. PANDAS is distinguished from other presentations of childhood-onset OCD by the acuity of its onset and a relapsing–remitting course of symptoms [3]. These unique clinical features raise the question of whether the long-term outcome of this subgroup differs from idiopathic or non-PANDAS OCD.

Estimated to affect about 0.1–3.6% of the general population, pediatric-onset OCD is one of the most common mental illnesses affecting childhood [4, 5]. Recent long-term follow-up studies of pediatric-onset OCD found rates of persistence into young adulthood ranging from 41 to 56% [4, 6–8]. As these studies did not examine the effects of an acute versus subacute onset of obsessive–compulsive symptoms, it is possible that data from children with PANDAS were included in the analyses. To date, however, no studies have examined longitudinal course and outcome of patients meeting criteria for PANDAS.

PANDAS is hypothesized to be etiologically similar to Sydenham chorea, in which cross-reactive antibodies form in response to a GAS infection in a genetically susceptible host [1]. As one of the manifestations of acute rheumatic fever, Sydenham chorea is characterized by choreoathetoid adventitious movements, failure to sustain tetanic contractions, and a variety of behavioral symptoms, particularly OCD and emotional lability [9]. Sydenham chorea is described as a subacute illness with a single symptomatic episode lasting 7–10 months. However, subsequent symptom recurrences are reported by 13–42% of patients, suggesting that Sydenham chorea might also be conceptualized as a relapsing–remitting disorder [9–13]. Given the commonalities of etiology and pathogenesis, the natural history of PANDAS has been postulated to mimic that of Sydenham chorea with a subacute initial illness followed by variable numbers of recurrences. However, prospective longitudinal assessment is needed to truly understand the clinical course of PANDAS. To obtain such data and better understand the prognosis of children with PANDAS, we conducted repeated evaluations of a cohort of children participating in a NIMH-Yale clinical trial [14]. Given the improvements observed at the end of the 6-month study period, we hypothesized that most subjects would report continued remission of their OCD symptoms, although we expected that at least some of the children would have periodic relapses.

Methods

Participants

Thirty-five participants were enrolled in a double-blind, randomized, placebo-controlled trial, conducted at the National Institute of Mental Health (NIMH) and the Yale Child Study Center between 2011 and 2013 [14]. At baseline, participants were required to meet criteria for PANDAS and to have moderate-to-severe OCD symptom ratings on the Children's Yale–Brown Obsessive Compulsive Scale (CY-BOCS) (total score ≥ 20) [15]. In addition, they needed to have had the concomitant onset of at least three other significant and impairing neuropsychiatric symptoms, thus meeting criteria for pediatric acute-onset neuropsychiatric syndrome (PANS) as well. Exclusion criteria for study participation were (1) a history of Sydenham chorea or acute rheumatic fever, (2) symptoms consistent with autism spectrum disorder or schizophrenia, (3) severe physical, behavioral, or psychiatric symptoms that would prevent study participation, and (4) prior corticosteroid or immunomodulatory therapy for PANDAS. The parents of participants provided informed consent, and participants provided written assent when applicable (age ≥ 7 years). Institutional Review Boards at both the NIMH and the Yale Child Study Center approved the study (NCT01281969), which allowed for periodic telephone contact by NIH investigators to assess general health and PANDAS symptoms for up to 5 years following enrollment in the RCT.

Post randomized controlled trial (RCT) follow-up

Follow-up data were collected via one or two semi-structured telephone interviews between NIH clinicians and the parents of participants. Five members of the NIH team conducted interviews, including two child psychiatrists, a social worker, a pediatric nurse practitioner, and a psychiatric nurse. Information regarding general health, mental health, medication and treatment utilization, obsessive–compulsive symptom exacerbations, other neuropsychiatric symptoms, and current functioning was obtained. Information regarding diagnoses (including GAS infection), symptoms, and treatments were based on parent report; if the parent reported an interval GAS infection, the interviewer inquired further to determine the nature of the infection (e.g., pharyngitis) and how it was determined (e.g., throat culture). Clinical judgment was used in determining symptom severity and functional impairment. Symptom exacerbations were broadly defined as a noticeable increase in any or all of a child's previous PANDAS symptoms lasting for a period of at least 24 h. No standardized instruments were used to assess symptoms or functional impairment during the follow-up phone interviews; during the RCT, formal assessments of OCD symptom severity and functional impairment were made using the Child Yale–Brown Obsessive Compulsive Scale (CY-BOCS) and Clinical Global Impressions-Improvement (CGI-I) and those instruments are referenced in this manuscript for comparative purposes. For a more detailed description of psychiatric and laboratory assessments and a more detailed description of the study population, please see Williams et al. [14].

Phone interviews were conducted in two waves, the first in the Fall 2013/Winter 2014, the second in Fall 2015/Winter 2016. Families whose children enrolled in the RCT after April 2013 ($n = 5$) were not contacted during the first wave of phone interviews. All other families were contacted twice; interviews were completed with three families at Wave 1 only, and two families at Wave 2 only. Two participants could not be reached during either interview wave and were considered lost to follow-up. At the time of the last in-person assessment (week 24), one of these participants was experiencing clinically significant OCD symptoms, and the other participant was experiencing subclinical OCD symptoms; these children did not appear to systematically differ from those that participated in our follow-up telephone assessments. Data from the remaining 33 participants (94% of the cohort) are reported here. All had at least one telephone interview, and 23 had two telephone interviews.

Results

General and mental health

The final follow-up telephone interview occurred between 2.2 and 4.8 years (mean 3.3 ± 0.7 years) after study entry (hereafter referred to as study baseline or baseline evaluation). Age at final follow-up ranged from 7.5 to 17.6 years (mean 12.6 ± 2.5 years). New medical diagnoses included: Lyme disease ($n = 2$), seizure disorder ($n = 1$), common variable immune deficiency ($n = 1$), growth hormone deficiency ($n = 1$), bleeding disorder ($n = 1$), and obstructive sleep apnea ($n = 1$) (see Table 1).

Table 1 Overall health

	Number	Percentage
New diagnoses		
Lyme disease	1	3
Seizure disorder	1	3
Common variable immune deficiency	1	3
Growth hormone deficiency	1	3
Bleeding disorder	1	3
Obstructive sleep apnea	1	3
ADHD	6	18
Anxiety, depression or phobia	5	15
Chronic tic disorder or OCD	3	9
General functioning		
"Very good" or "Excellent"	21	64
"Moderate" or "Good"	10	30
"Poor"	2	6

Numbers and percentages here are out of the total sample ($n = 33$ participants). New diagnoses refer to diagnoses made since a child completed the RCT. General functioning refers to a child's overall functional status in the 6 months preceding the follow-up phone interview

ADHD attention-deficit/hyperactivity disorder, *OCD* obsessive–compulsive disorder

Six children underwent tonsillectomy during the follow-up period. One child was hospitalized for an asthma exacerbation. Twelve children had received one or more vaccination. Vaccinations included seasonal influenza vaccine as well as routine scheduled childhood vaccines. Vaccines were generally well tolerated and were not reported to have exacerbated PANDAS symptoms. One child was reported to have a PANDAS relapse 2 weeks following a diphtheria, tetanus, and pertussis (DTaP) vaccination, but it is not clear that the two events were linked.

Eleven (33%) children were given at least one new psychiatric diagnosis after the clinical trial was concluded. Six (18%) were diagnosed with attention-deficit/hyperactivity disorder (ADHD); three (9%) with anxiety disorder; one (3%) with depression; one (3%) with specific phobia; and one (3%) with chronic tic disorder.

Treatments

Several treatment modalities were utilized during the observation period. At study baseline, all children were prescribed a prophylactic dose of antibiotics for the 6-month duration of the treatment trial, and 32 (97%) elected to continue prophylaxis following completion of the active phase of the study (see Fig. 1a). At final follow-up, 22 (67%) children continued antibiotics prophylaxis, with penicillins being the most common class of antibiotic utilized (see Fig. 1b). Throughout the follow-up period, eight children had at least

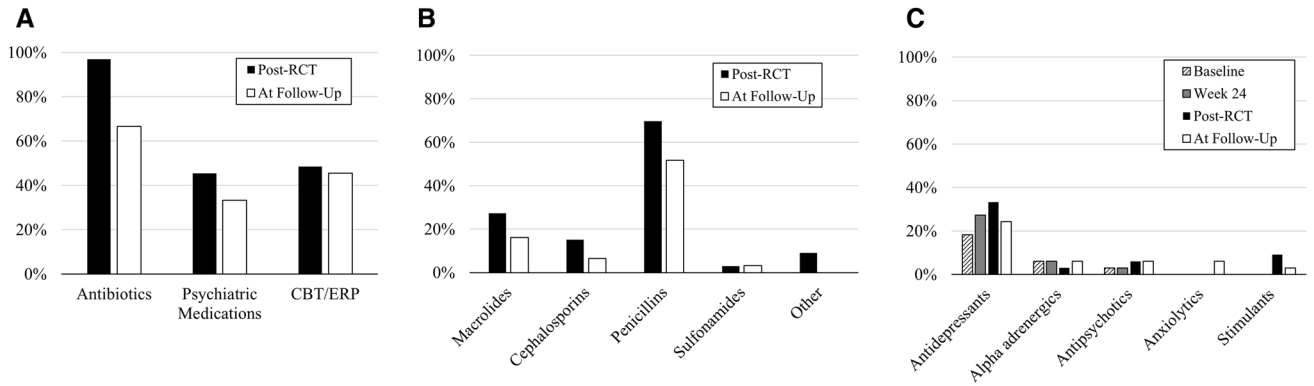

Fig. 1 Depicts treatment utilized by participants during the post-RCT (interim) period and at the time of phone follow-up. **a** Treatments utilized ($n = 33$). Most children took prophylactic antibiotics after participating in the RCT. About half engaged in structured psychotherapy or were treated with psychiatric medication. **b** Antibiotic class ($n = 31$) depicts the various classes of antibiotics used in the post-RCT period and at the time of follow-up. **c** Psychiatric medications ($n = 33$) Depicts psychiatric medication use at RCT entry and completion as well as during the post-RCT interim period and at the time of follow-up. Antidepressants were the most commonly used medication class; all children treated with antidepressants were taking selective serotonin reuptake inhibitors, with the exception of one child who was taking mirtazapine

one documented GAS infection. For six of these children, prophylactic antibiotics had been discontinued prior to the infection. Two others were reported to be taking amoxicillin/clavulanic acid at the time of infection and continued the same regimen.

Approximately two-thirds of children either continued or engaged in care with a mental health provider after study participation. However most did not require ongoing care for the full duration of follow-up, and six (18%) had discontinued all therapies prior to the final evaluation (see Fig. 1a). Throughout the follow-up period, a total of 15 participants (45%) took a psychiatric medication. Seven of these 15 children had begun taking medication prior to enrolling in the study (see Fig. 1c). The remaining 8 children began treatment at various times during the follow-up period. Participation in some form of cognitive-behavioral therapy (CBT), typically exposure and response prevention therapy (ERP), was also common, as it had been recommended by the study team for all children with ongoing or recurrent symptoms. Seventeen (52%) children received CBT and 5 children (15%) received other psychotherapy (e.g., play therapy). In total, 22 children (67%) participated in psychotherapy for at least a portion of the follow-up period, with 16 (48%) children remaining in treatment at the time of final evaluation.

Course of illness

At study completion (week 24), 25 of the 33 participants in this study were rated as "much" or "very much" improved over baseline on the Clinical Global Impressions-Improvement rating scale (CGI-I) [14, 16]. Overall, the children were doing well, with mean CGI-S Severity and CY-BOCS scores in the "mild" range (for a more detailed description of symptom severity and clinical course during the RCT, please see Williams et al. [14]). At the time of follow-up, overall outcomes were also markedly positive, with 21 participants (64%) reporting general functioning over the preceding 6 months to be "very good" or "excellent." Ten participants (30%) reported "moderate" to "good" functioning, and only two participants (6%) were reported to have "poor" overall functioning (Table 1). One participant with poor functioning was currently experiencing a symptom exacerbation, while the other participant had developed a chronic course of psychiatric symptoms. Interestingly, neither participant had responded to IVIG during the blinded phase of the study.

In total, 24 (72%) participants were reported to have had at least one symptom exacerbation during the follow-up period (Table 2). A total of 59 exacerbations were reported (median: 1 exacerbation, interquartile range 0–3 exacerbations, range 0–12). Of the participants who experienced PANDAS exacerbations, 12 (50%) experienced one exacerbation; eight participants (33%) experienced two or three exacerbations; four participants (17%) experienced ≥ 4 exacerbations. The remaining nine (27%) participants did not experience any exacerbations of PANDAS symptoms.

Table 2 PANDAS exacerbations

	Number	Percentage
Exacerbations ($n = 24$ participants)		
One exacerbation	12	50
Two to three exacerbations	8	33
Four or more exacerbations	4	17
Timing of exacerbations after baseline ($n = 22$ participants) (years)		
< 1	7	32
1–2	8	36
> 2	7	32
Duration ($n = 21$ exacerbations) (weeks)		
≤ 1	8	38
2–4	5	24
8–12	4	19
≥ 16	4	19
Potential precipitants ($n = 47$ exacerbations)		
GAS infection	9	19
GAS exposure	5	11
Non-GAS infection	10	21
Socio-environmental event	1	2
No clear precipitant	22	47
Treatments ($n = 59$ exacerbations)		
Antibiotics	36	61
IVIG	15	25
Psychotherapy	7	12
Psychiatric medication	6	10
NSAIDS	18	30
No treatment	4	7

Numbers and percentages here are out of the children in the sample who experienced an exacerbation of symptoms after completing their participation in the RCT

Exacerbation duration was reported by 12 participants for a total of 21 exacerbations. Potential precipitants of exacerbations were reported for 47 exacerbations and treatments utilized were reported for all exacerbations. Exacerbations were often treated with multiple treatment modalities, thus percentages in the Treatments box exceed 100%

GAS Group A streptococcal infection; *IVIG* Intravenous immunoglobulin; *NSAIDS* Non-steroidal anti-inflammatory drugs

Data regarding the time that elapsed between study baseline and the first exacerbation are available for 22 of the 24 participants who reported experiencing an exacerbation. These participants experienced their first exacerbation an average of 1.65 ± 1.08 years after study baseline (Table 2). No correlation was found between an earlier onset of the first exacerbation and an increased number of exacerbations, nor between severity of initial episode and likelihood of subsequent exacerbations. Exacerbation episode duration was available for 12 participants with 21 exacerbations, and ranged from 1 day to ≥ 24 weeks, with a mean duration of

5.3 ± 6.1 weeks (see Table 2). Precipitating factors were identified for 47 exacerbations. Nine flares (19%) were preceded by a documented GAS infection, and five (11%) were reported to occur after exposure to GAS (e.g., sibling had a GAS infection). Ten (21%) non-GAS infections were temporally associated with the onset of a flare, and one exacerbation (2%) was associated with a socio-environmental event (specifically, a trip to the doctor's office). However, 22 exacerbations (47%) had no clear precipitant.

A variety of treatments were used to address symptom exacerbations. Antibiotics were the most common treatment, and were utilized in 36 (61%) exacerbations. IVIG was used to treat 15 (25%) exacerbations which affected 10 children. Exacerbations treated with IVIG were not reported to be more severe than those treated with antibiotics. Non-steroidal anti-inflammatory drugs (NSAIDS) were used by six families in the treatment of 18 exacerbations (30%). Four families reported using psychiatric medications to treat 6 exacerbations, and 6 families (7 exacerbations) reported using psychotherapy to address symptoms. Multiple treatment modalities were frequently utilized simultaneously to address the same PANDAS exacerbation. Four exacerbations occurring among 3 children went untreated; all were of mild severity and resolved without treatment in less than 1 month.

Symptoms at follow-up

At follow-up, most children were improved from study baseline. Twenty-nine of 33 (88%) participants were experiencing either no OCD symptoms ($n = 18$, 55%) or only subclinical symptoms ($n = 11$, 33%) (Fig. 2). Of the four children with clinically significant OCD symptoms, one child was reported to be experiencing a symptom exacerbation at the time of follow-up, one child had discontinued all treatments despite having unresolved symptoms, and two children had persistent OCD symptoms and remained in treatment.

Discussion

At follow-up, an average of 3.3 years after baseline evaluation, 88% of participants were in complete or nearly complete remission. However, most children (72%) had at least one exacerbation of PANDAS symptoms during the follow-up period. Exacerbations were generally short-lived and less severe than the baseline episode. A variety of treatment modalities were used to address exacerbations; combinations of antibiotics and immunomodulatory therapies or immunotherapies plus CBT appeared to have optimal impact.

These findings are in keeping with the published literature on Sydenham chorea and with previous retrospective reviews comparing children with PANDAS and non-PANDAS OCD and tics. A recent study of 142 participants with Sydenham chorea showed similar variability in clinical course. During the 10 year observation period, 76% of participants experienced only one episode of chorea, 18% experienced two episodes, 6% experienced three episodes, and 0.5% experienced four episodes [17]. Moreover, while 30% of PANDAS exacerbations were associated with GAS infection or exposure, and an additional 20% were thought to be triggered by non-streptococcal illness, approximately half had no identifiable infectious trigger. This parallels findings in Sydenham chorea, where exacerbations following non-GAS triggers are not uncommon, and are thought to represent generalization of the misdirected immune reactivity [18, 19]. It should be noted that the proportion of PANDAS exacerbations associated with GAS infection may be higher in community samples in which children are not receiving prophylactic antibiotics (as the majority of our sample did for at least of portion of the follow-up period) or among children who have not undergone tonsillectomy (six study participants had a tonsillectomy during the follow-up period).

Previous work suggests that children with PANDAS experience a more episodic course than children with

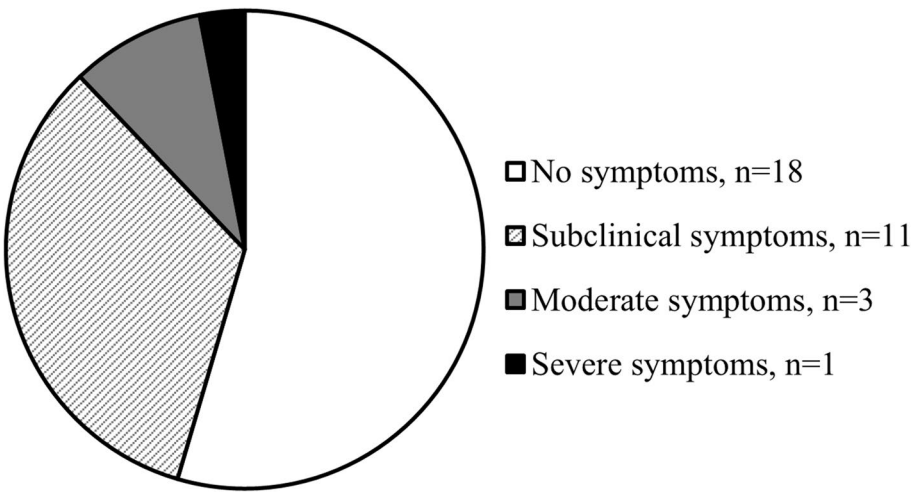

Fig. 2 OCD symptom severity at the time of follow-up ($n = 33$)

non-PANDAS OCD and are perhaps more likely to achieve remission of symptoms. A 2012 outpatient study comparing children with PANDAS ($n = 41$) to children with tics, OCD, or both ($n = 68$) found that children with PANDAS were significantly more likely to experience definite remissions of symptoms [20]. Although the study was limited to cross-sectional data, the results suggest that PANDAS may have a less chronic course than other presentations of childhood-onset tics and OCD [4]. Our findings support this assertion. Most children in this cohort had few residual obsessive–compulsive or ancillary neuropsychiatric symptoms, and no more than minimal or mild impairment at follow-up. Only three children had a chronic course of illness, with ongoing OCD and phobia symptoms in one child; anorexia, OCD, and emotional lability in another; and anxiety, emotional lability, and significant irritability/aggression in the third child. Retrospective review of their medical charts revealed no characteristic features that distinguished them from other study participants. Additional research is needed to determine the factors influencing the longitudinal course of PANDAS.

An important finding of our study was the observation that vaccinations did not trigger symptom exacerbations in this group of children with a history of PANDAS. A recent study found a weak association between vaccine administration and onset of anorexia, OCD, and tics [21]. However, NIMH clinicians have routinely recommended that children with PANDAS receive the influenza vaccine and other scheduled vaccinations as recommended by the Centers for Disease Control and Prevention (CDC), because it is thought that the risks of these illnesses, and the possibility of the illnesses themselves triggering a PANDAS exacerbation, outweigh any theoretical vaccine-associated risks. Results of this study support this practice and confirm that, at least in this cohort of PANDAS patients, vaccinations were safe and well-tolerated.

As noted above, the long-term outcome of this cohort of children with PANDAS was better than has been reported for children with non-PANDAS OCD, in whom remission rates are estimated to range from 41 to 56% with continued treatment [4, 6–8]. In several of these studies, the presence of a concomitant tic disorder was positively associated with rates of remission of OCD, raising the question of whether the children might have had PANDAS [7, 8]. Other features that have been found to be associated with increased likelihood of symptom remission are decreased OCD severity at assessment, and the absence of hoarding symptoms [7]. Assessment of additional clinical correlates associated with remission remains important for future longitudinal studies of PANDAS, along with factors which impact the time to remission.

Limitations and future directions

This study is limited by its dependence on telephone interviews with parents rather than in-person clinical evaluations of the affected children. Timing and duration of symptom exacerbations may have been subject to recall bias. Additionally, the semi-structured interviews were conducted by several clinicians over a multi-year period, resulting in some variation in clinical content. To better characterize the nature of PANDAS exacerbations, and particularly their precipitating factors, future longitudinal studies might employ more frequent evaluations and in-person assessments during the symptomatic periods.

We report here the results from the first study of long-term treatment outcomes from PANDAS patients treated with IVIG. Future prospective studies of larger cohorts of participants with PANDAS would be useful not only in confirming the results of this study, but also in examining specific biomarkers and/or symptoms that might be associated with the natural history of this illness. Examining the relationship between specific symptoms (e.g., food restriction, contamination fears, separation anxiety, tics, etc.) and expanding the study population to include children with similar disorders, such as Avoidant/Restrictive Food Intake Disorder (ARFID), tic disorders, or separation anxiety disorder, might also illuminate and improve our understanding of the role of environmental precipitants, such as streptococcal infections, in childhood mental illness.

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Compliance with ethical standards

Conflicts of interest Dr. Leckman has received grant or research support from the National Institutes of Health, the UBS Optimus Foundation, and the Open Road Alliance. He has served on the advisory boards/DSMB of the Brain and Behavior Research Foundation, the National Organization for Rare Disorders, Fondazione Child, the European Muilticentre Tics in Children Studies, and How I Decide. He has authored the Yale Global Tic Severity Scale (YGTSS) assessment tool, which is open access. He has received honoraria from the European Society for the Study of Tourette Syndrome and the Brazilian Psychiatric Association. He has received royalties from John Wiley and Sons, McGraw Hill, and Oxford University Press. He has received travel expenses from the University of Illinois Chicago, Cornell Weill Medical College, the Medical University of South Carolina, Rutgers University, the British Academy, and the Brazilian Psychiatric Association. He has received additional support from Anne Çocuk Eğitim Vakfi (AÇEV; Mother Child Education Foundation) and private donors. Drs. Williams, Swedo, Farmer, Grant, Hommer, and Mss. Leon, D'Souza, and Kessler report no biomedical financial interests or potential conflicts of interest.

Ethical standards All research was conducted in accordance with the ethical standards described by the Declaration of Helsinki and according to standards established by the National Institute of Health's Combined NeuroScience Institutional Review Board. All participants gave assent and their parent or guardian provided informed consent prior to study participation.

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